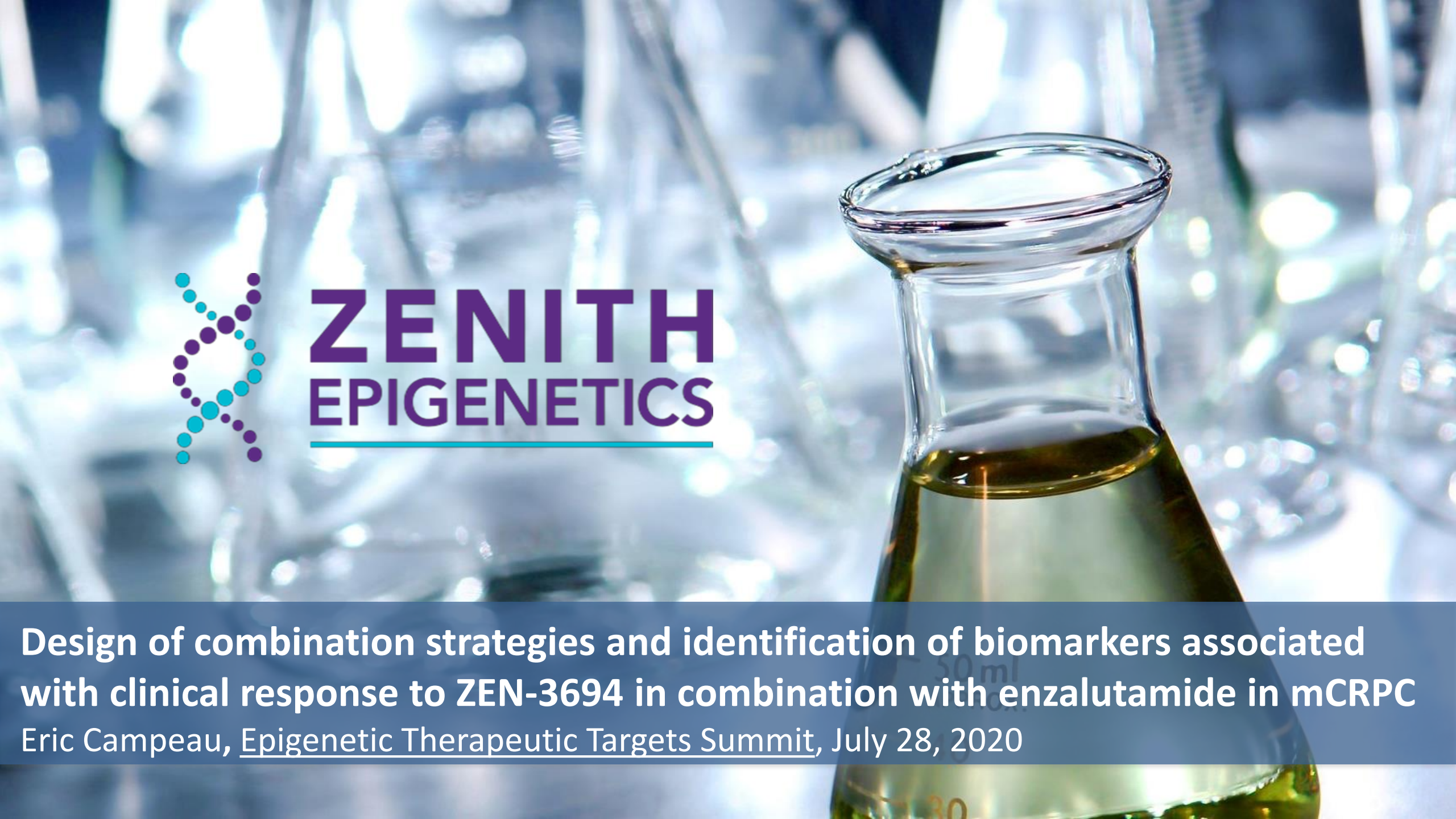


ZENITH EPIGENETICS

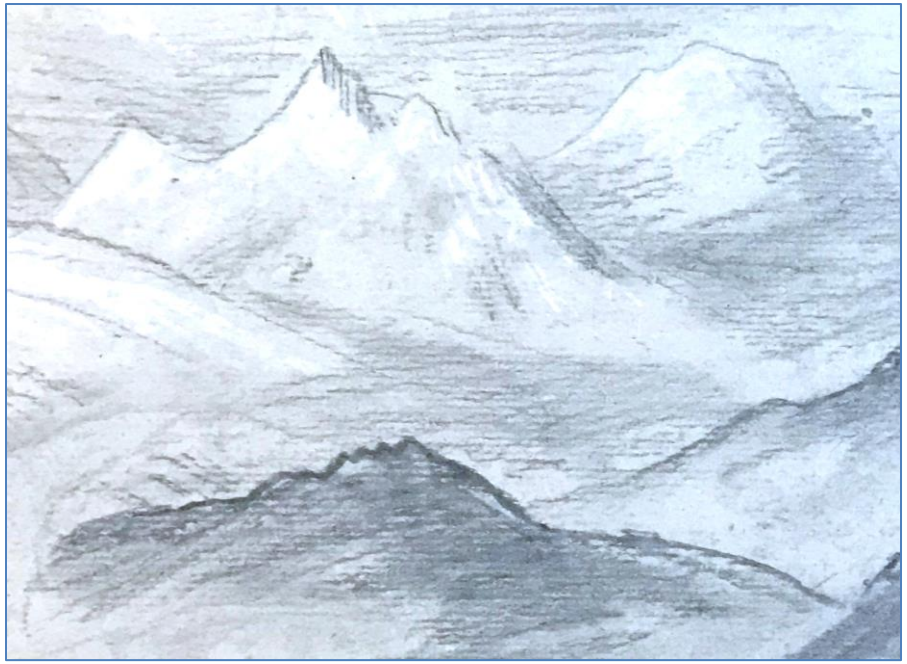
Design of combination strategies and identification of biomarkers associated with clinical response to ZEN-3694 in combination with enzalutamide in mCRPC

Eric Campeau, Epigenetic Therapeutic Targets Summit, July 28, 2020

Changes in epigenetic landscape in response to anti-cancer treatments

ZENITH EPIGENETICS

“Mountain” Transcriptional Program



Epigenetic regulation

“Plain” Transcriptional Program

- **Epigenetic regulation allows rapid adaptation to changes in (tumor) environment**

⇒ No required changes in DNA

⇒ Dynamic, reversible

- **Use of combination strategies for optimal therapeutic efficacy**

⇒ Combination of epigenetic inhibitors with optimal agents

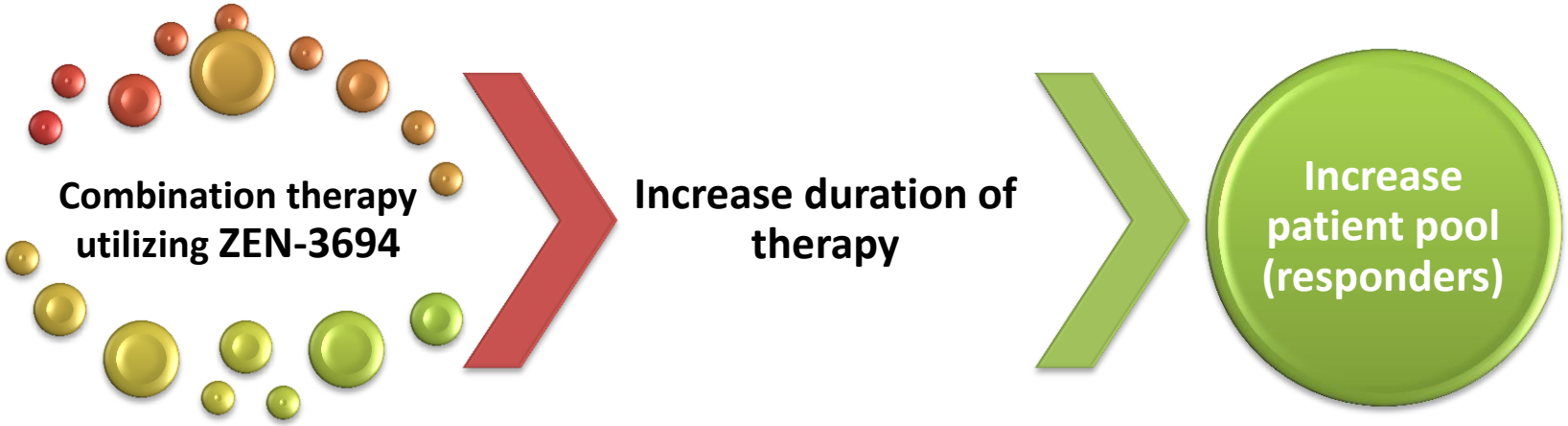
Seekpng.com

Our Approach: Making Great Drugs Work Better & Longer

Combinations with ZEN-3694 to <u>prevent</u> and <u>reverse</u> resistance to standard of care therapies

Current possibilities include:

- Androgen receptor signaling inhibitors (ARSIs)
- PARP inhibitors
- PD-1/PD-L1 monoclonal antibodies (checkpoint inhibitors)
- CDK4/6 inhibitors



Selection of the BET inhibitor ZEN-3694 with ideal combinatorial properties

> 1800 synthesized compounds
(incl. different chemical scaffolds)

↓

23 lead compounds
Preclinical off-target/PK/TOX: *in vitro* and *in vivo*

↓

6 DC compounds
Rat 5 day tox + xenografts

↓

ZEN-3694 selected

Best 3 Lead Compounds

Compound	BRD4 (BD1)	PK (Rat 10 mg/kg)			Efficacy (21 days, 60 mg/kg QD)	Adverse Events
		Half-life	C_{max}	AUC		
ZEN-3694	+++	++	+	+	+++	• Mild reduction in PLT
ZEN-3803	++	++	++	++	+++	• Moderate PLT reduction
ZEN-3717	++	+++	+++	+++	+++	• Severe PLT reduction • Decreased in body weight

PLT= platelet

ZEN-3694 with a moderate half-life showed better or similar efficacy in xenografts without tolerability issues

ZEN-3694 is best-in-class & clinically differentiated

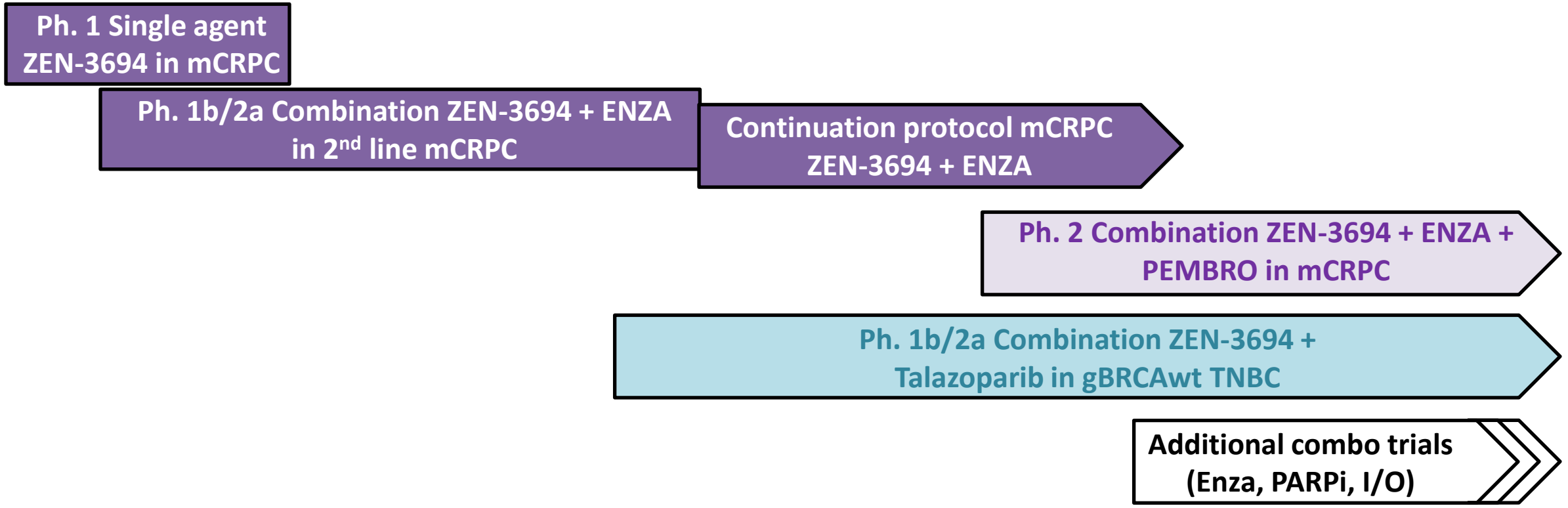
Other Clinical BETi

- Suboptimal benzodiazepine scaffold with poor pharmacological properties
- Off target toxicities
- CYP liabilities
- Thrombocytopenia DLT, require 1-2 weeks off, difficult to combine

Zenith's BETi (ZEN-3694)

- Orthogonal scaffold with very good pharmacological properties
- On target toxicity profile
- Minimal CYP liabilities
- Minimal thrombocytopenia liability, safety profile allows continuous dosing and combinations

Prioritization of combinatorial strategies with ZEN-3694



Selection of optimal combination agents and patient populations with unmet medical needs

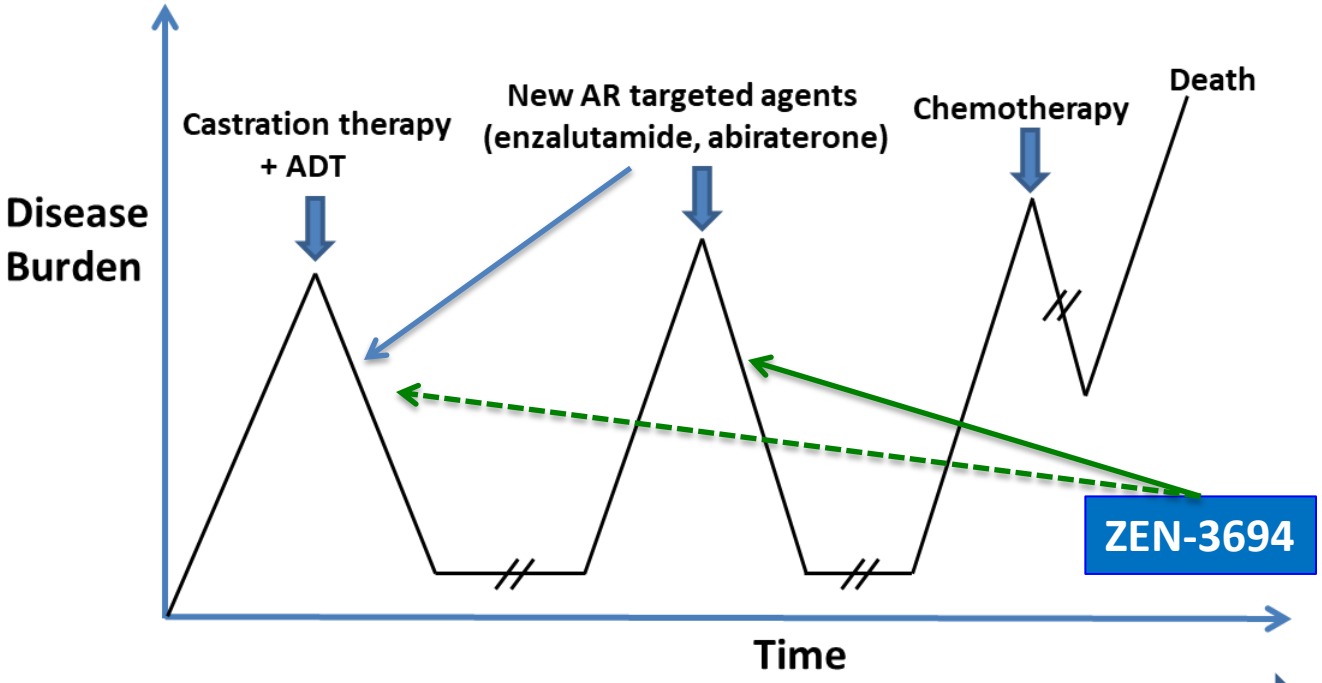
1) Metastatic castration-resistant prostate cancer (mCRPC)
⇒ **Combination ZEN-3694 + enzalutamide**
⇒ **Combination ZEN-3694 + enzalutamide + pembrolizumab (Q4 2020)**

2) Metastatic triple negative breast cancer (TNBC) patients **without** germline BRCA1/2 mutations (gBRCA1/2wt)
⇒ **Combination ZEN-3694 + talazoparib** (in collaboration with Pfizer)

A Phase 1b/2a Study of the Pan-BET Bromodomain Inhibitor ZEN-3694 in Combination with Enzalutamide in Patients with Metastatic Castration Resistant Prostate Cancer

(Aggarwal et al. Clin. Can. Res. 2020)

Castration-resistant prostate cancer (CRPC):
Disease progression and treatment algorithm



- **1st line AR signaling inhibitor (ARSI)**

⇒ Enzalutamide, apalutamide, darolutamide, abiraterone

⇒ Clinical benefits in several patients

- **2nd line ARSI post 1st line ARSI associated with lower activity**

⇒ Most patients progress between 3-6 mo

- **ARSI now prescribed in castration sensitive setting**

⇒ **Unmet need to prolong ARSI activity in castration sensitive and resistant settings**

Castration-sensitive → Castration-resistant

Non-metastatic → Metastatic

Restore AR signaling
(AR mutations and amplification, splice variants, androgen biosynthesis)

Bypass AR signaling
(GR up-regulation)

Alternate pathway (AR-)
(Transdifferentiation, AR-independent)

ZEN-3694 + enzalutamide can address multiple resistance mechanisms

Inhibits AR signaling

Inhibits GR signaling

Resensitizes cells to AR signaling

Phase 1b/2a: ZEN-3694 in combination with enzalutamide in mCRPC

(NCT02711956)

ZENITH EPIGENETICS

ESCALATION

ZEN-3694 + ENZA dose escalation

- Doses **36-144mg** daily

EXPANSION

ZEN-3694 + ENZA expansion #1

- Patients progressing on prior **ABI**
- Doses **48 mg** OR **96 mg** daily

ZEN-3694 + ENZA expansion #2

- Patients progressing on prior **ENZA**
- Doses **48 mg** OR **96 mg** daily

Inclusion criteria:

- Progression on prior ABI and/or ENZA (radiographic, clinical, PSA)
- No prior chemotherapy in castration-resistant setting
- On trial until radiographic or clinical progression (PCWG2)

- **75 patients dosed (35 pts in dose escalation, 14 in dose expansion #1, 26 in dose expansion #2)**
- **MTD not reached (36mg – 144mg daily dose range) → RP2D 96mg**
- **Clinical activity at well tolerated doses, prolonged dosing without dose interruptions/reductions**

Aggarwal et al. CCR 2020

ZEN-3694 related Grade 3 or 4 adverse events

On target tox profile and good tolerance of daily dosing

	36mg QD		48mg QD		60mg QD		72mg QD		96mg QD		120mg QD		144mg QD	
	n=4		n=21		n=6		n=6		n=30		n=4		n=3	
Grade	3	4	3	4	3	4	3	4	3	4	*3*	*4*	*3*	*4*
Decreased appetite									1					
Dehydration									1					
Fatigue			1						1					
GFR Decreased*									1					
Hypokalemia**							1							
Hypophosphatemia**					1		1							
Nausea									3					
Thrombocytopenia									2				1	
QT prolongation													1***	

*Patient previously had kidney resected due to RCC

**Hypokalemia and hypophosphatemia resolved with oral potassium and phosphorus

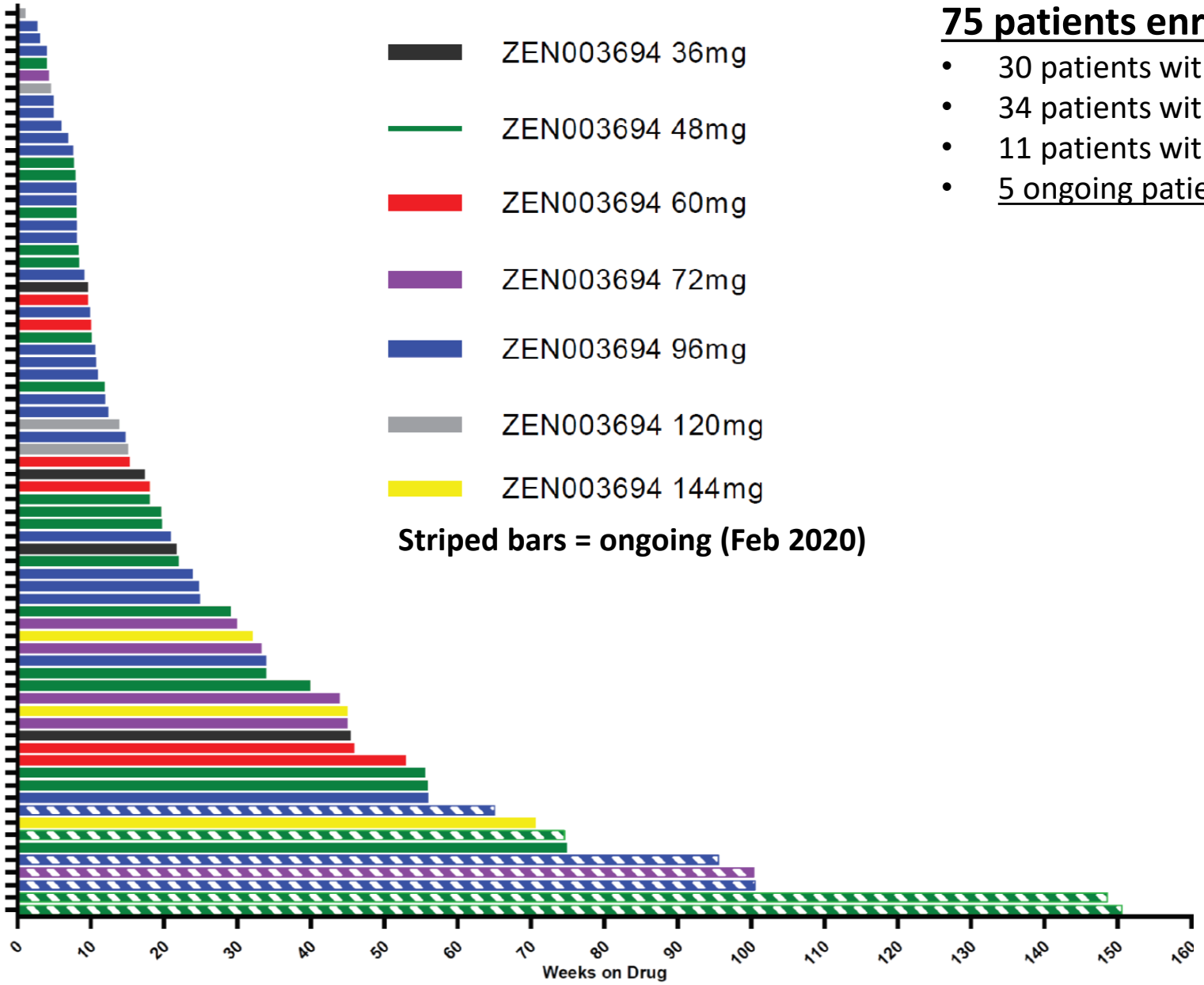
*** Patients had QT prolongation prior to treatment, QT prolongation resolved and patient continued treatment

Grade 1-2 AE mainly GI related toxicities

Grade 3-4 thrombocytopenia in 3/75 (4%) patients

Time on Study ZEN-3694 + enzalutamide in mCRPC patients

(NCT02711956)- Data cutoff February 2020



75 patients enrolled

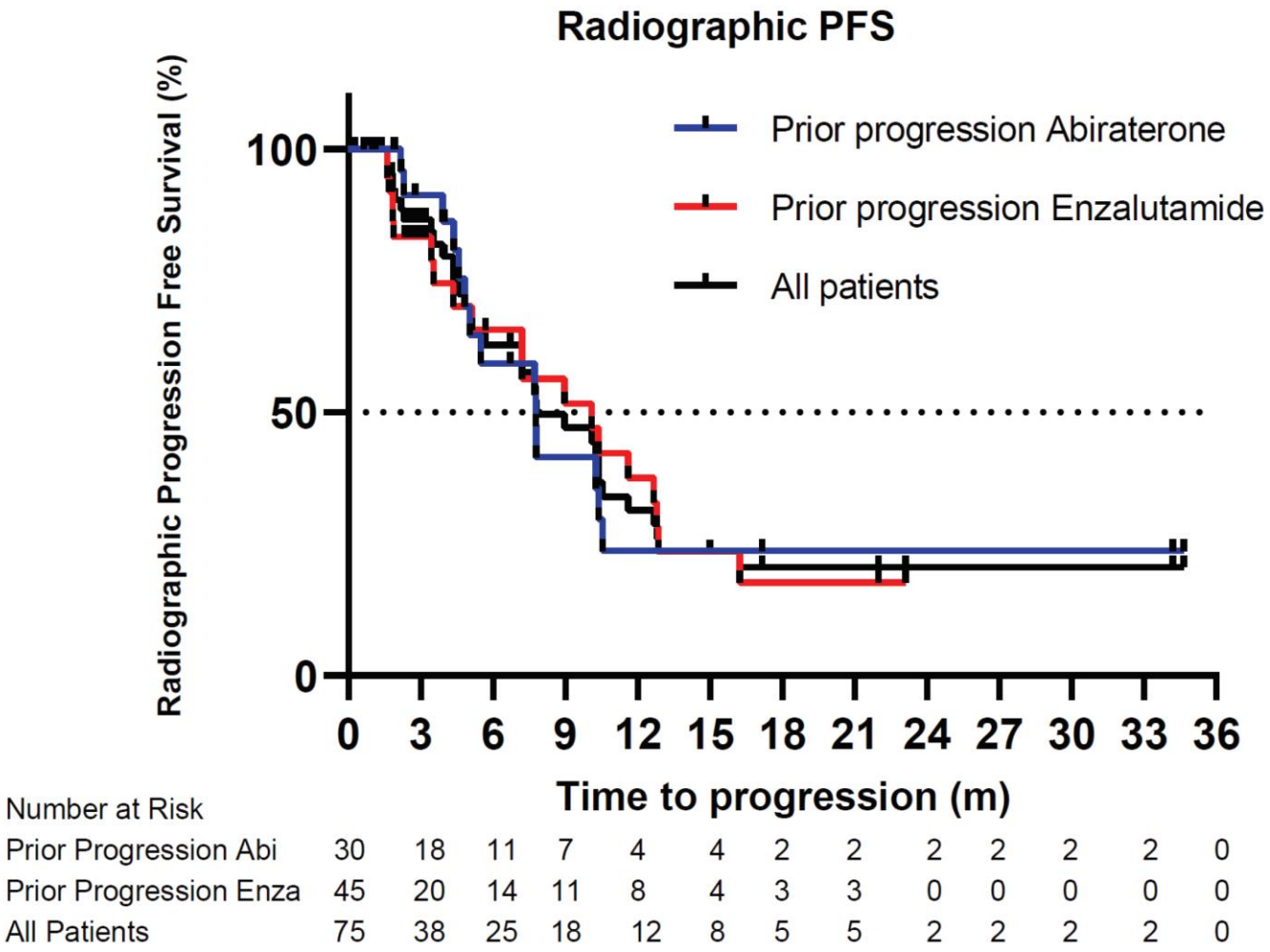
- 30 patients with prior ABI progression (19 with rPD on ABI)
- 34 patients with prior ENZA progression (18 with rPD or cPD on ENZA)
- 11 patients with prior ABI + ENZA progression (5 with rPD on ABI/ENZA)
- 5 ongoing patients (July 2020) (from 1.7 to 3.3 years On-Treatment)

rPD = radiographic progressive disease
cPD = clinical progressive disease

Aggarwal et al. CCR 2020

Prolonged time to radiographic progression vs. historical 2nd line ARSI

Similar mPFS between ABI and ENZA progressors



Median $rPFS_{ALL\ patients}$ = 9.0 mo
Median $rPFS_{ABIprogressors}$ = 7.8 mo
Median $rPFS_{ENZAprogressors}$ = 10.1 mo

Historical median rPFS* = 3 to 6mo
*2nd line single agent ARSI

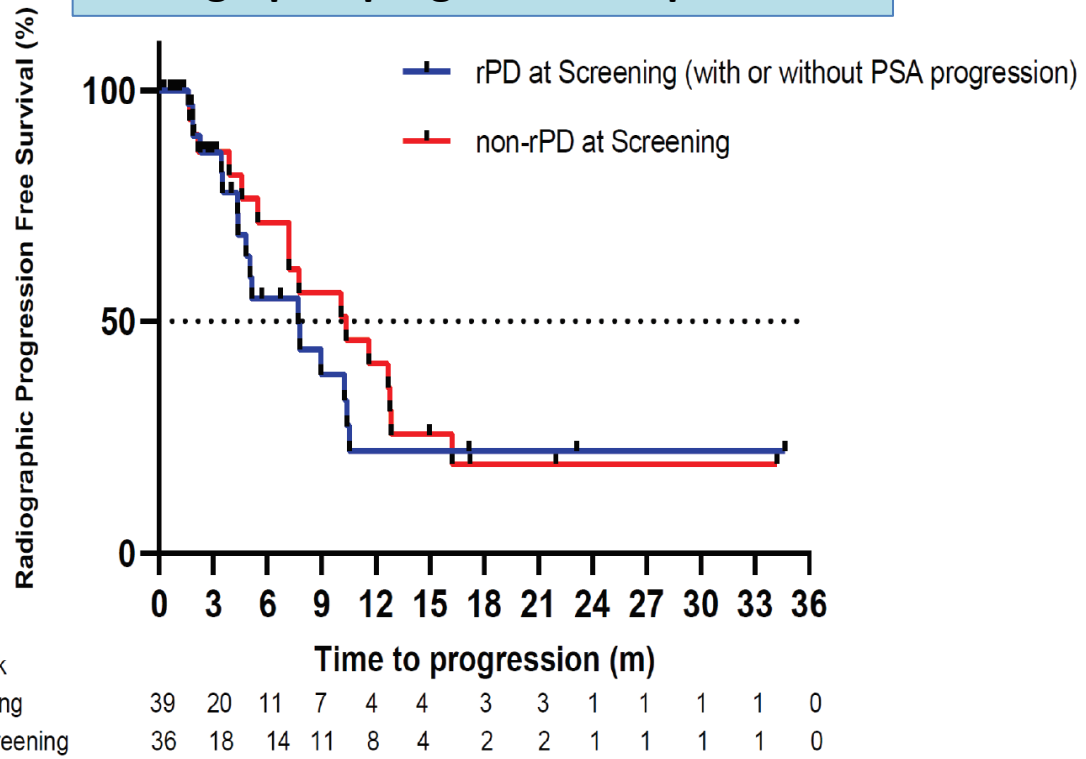
rPFS = radiographic progression free survival

Evidence of ZEN-3694 activity in both Post-ABI and Post-ENZA settings

Aggarwal et al. CCR 2020

Patients with clinical factors associated with aggressive disease benefited from combination therapy

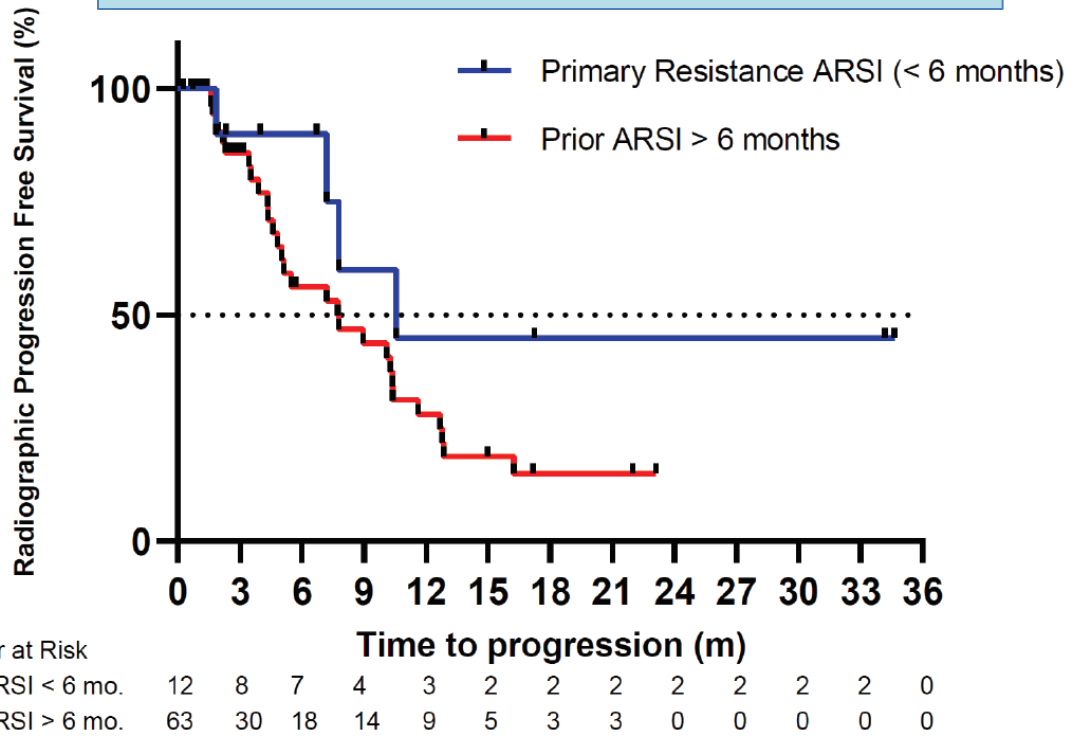
Radiographic progression on prior ARSI



Number at Risk													
rPD at Screening	39	20	11	7	4	4	3	3	1	1	1	1	0
non-rPD at Screening	36	18	14	11	8	4	2	2	1	1	1	1	0

Median $rPFS_{rPD}$ = 7.8 mo

Primary/de novo resistance to 1st line ARSI



Number at Risk													
Prior ARSI < 6 mo.	12	8	7	4	3	2	2	2	2	2	2	2	0
Prior ARSI > 6 mo.	63	30	18	14	9	5	3	3	0	0	0	0	0

Median $rPFS_{1^{y}ARSI<6mo}$ = 10.6 mo

Evidence of clinical activity of ZEN-3694 in populations with clinical factors associated with poor responses to ARSI

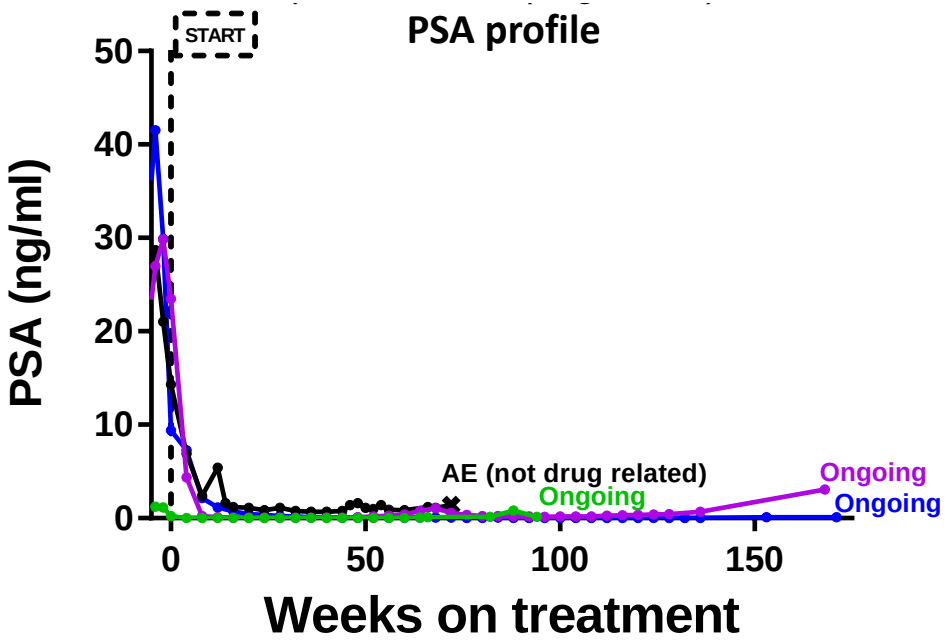
*Non-rPD = PSA and or clinical progression

Aggarwal et al. CCR 2020

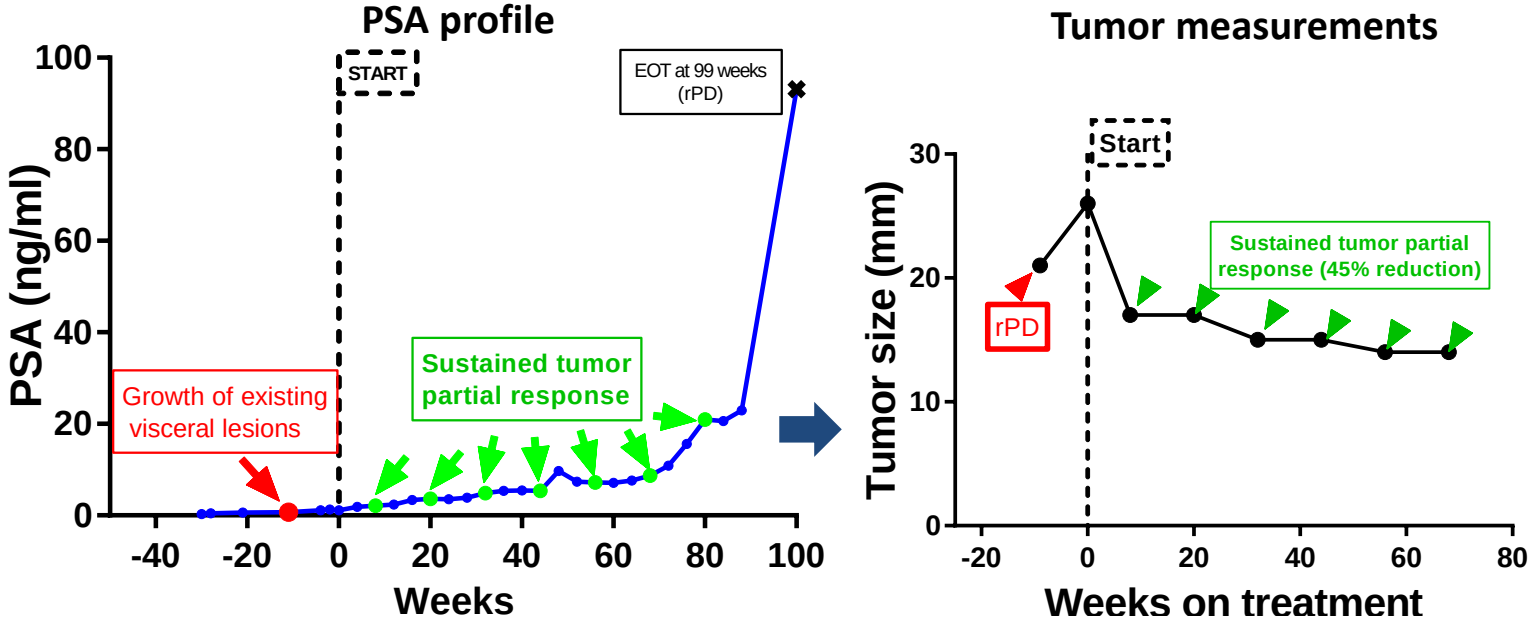
Examples of best responders #1

Sustained PSA90 or partial tumor response

Four patients with prolonged PSA90 responses
(3/4 patients ongoing)



Sustained tumor partial response of 1.8 years in patient with radiographic progression of visceral lesions on prior ENZA



FULL PAPER
Artificial Intelligence

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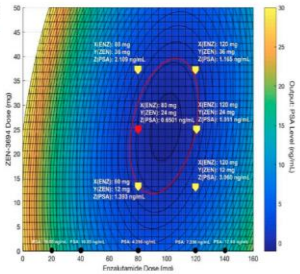
Modulating BET Bromodomain Inhibitor ZEN-3694 and Enzalutamide Combination Dosing in a Metastatic Prostate Cancer Patient Using CURATE.AI, an Artificial Intelligence Platform

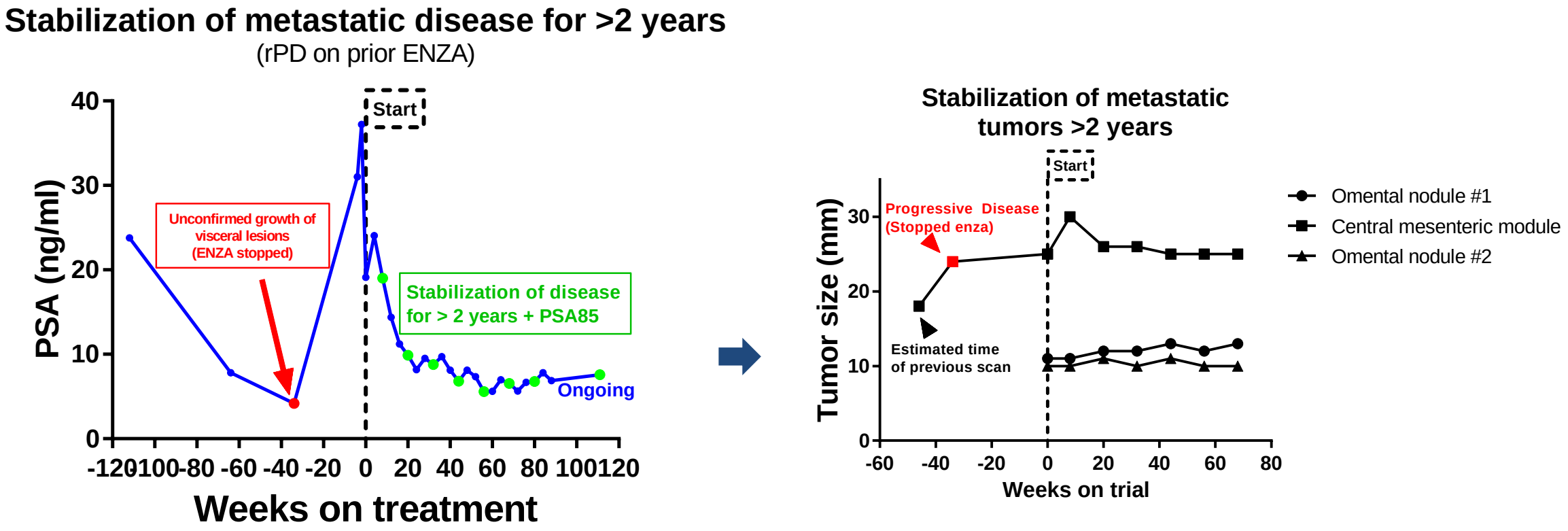
Allan J. Pantuck, Dong-Keun Lee, Theodore Kee, Peter Wang, Sanjay Lakhotia, Michael H. Silverman, Colleen Mathis, Alexandra Drakaki, Arie S. Belldegrun, Chih-Ming Ho,* and Dean Ho**



Pantuck et al. 2018, Aggarwal et al. CCR 2020 + unpublished results

Examples of best responders #2

Clinical and radiographic progression on prior ENZA - Stabilization of disease with PSA85 > 2 years



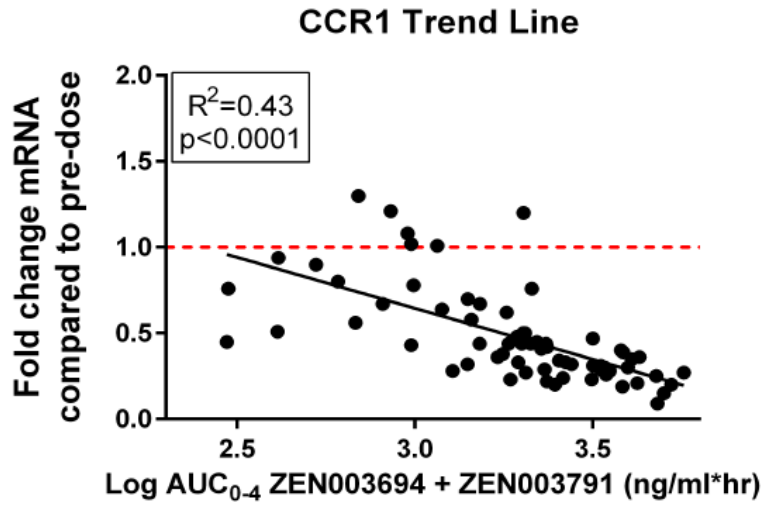
Aggarwal et al. CCR 2020 + unpublished

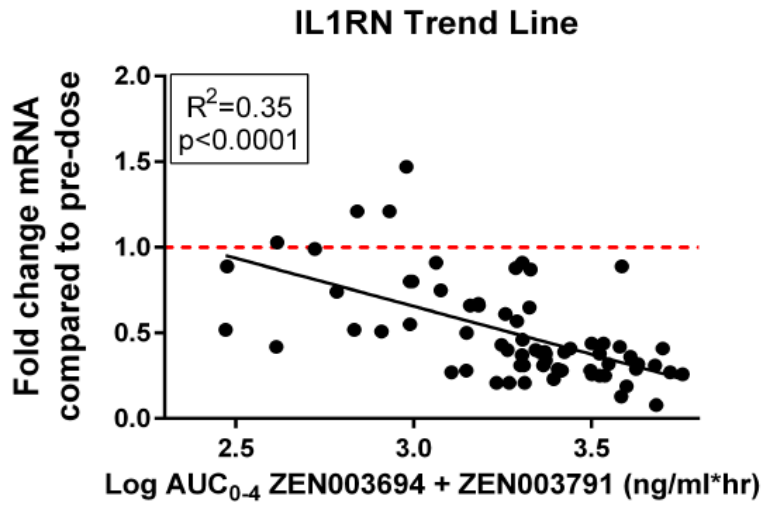
Detection of ZEN-3694 target engagement in whole blood and tumor biopsies

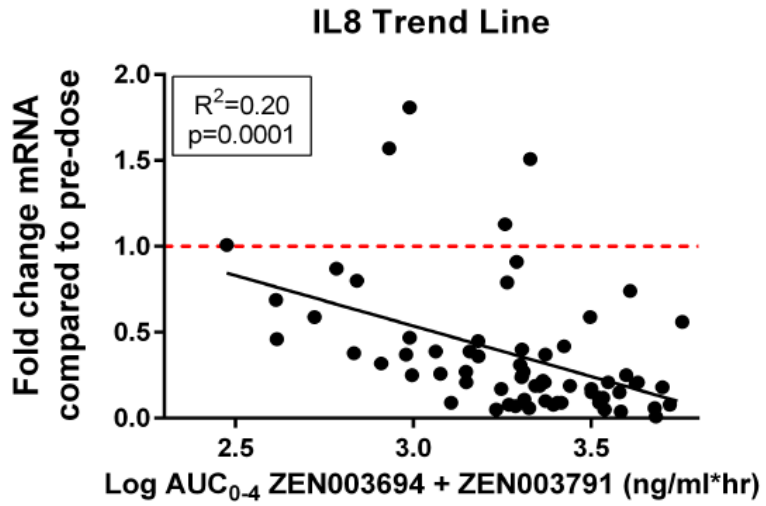
Aggarwal et al. CCR 2020

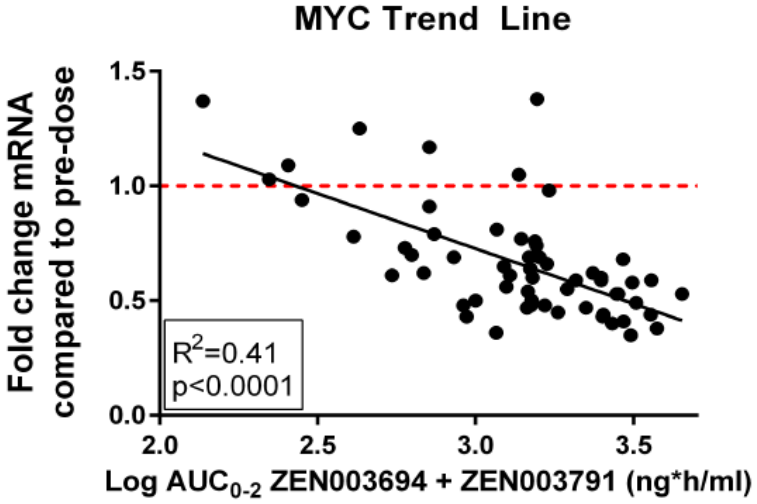
Detection of target engagement in whole blood

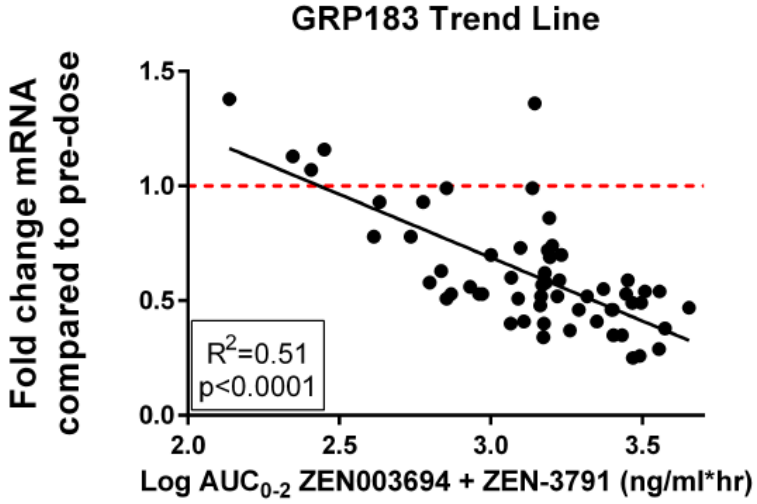
Significant exposure-dependent target engagement for 5 PD markers

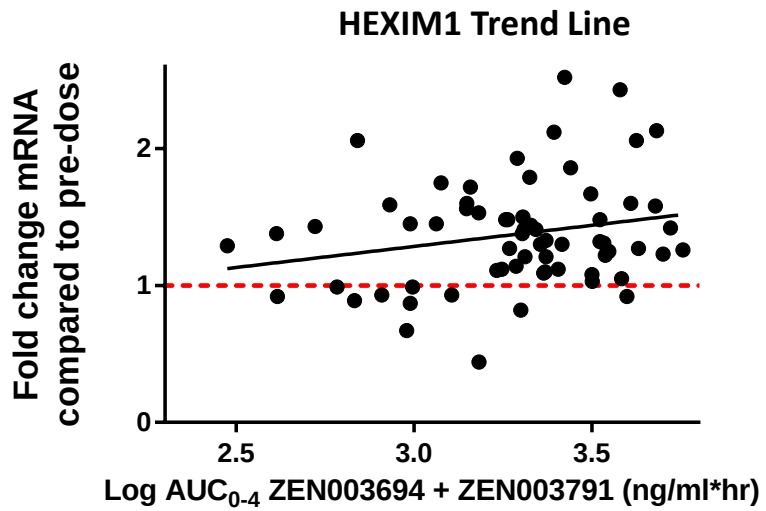












Target engagement detected at all doses (48-144mg ZEN-3694)

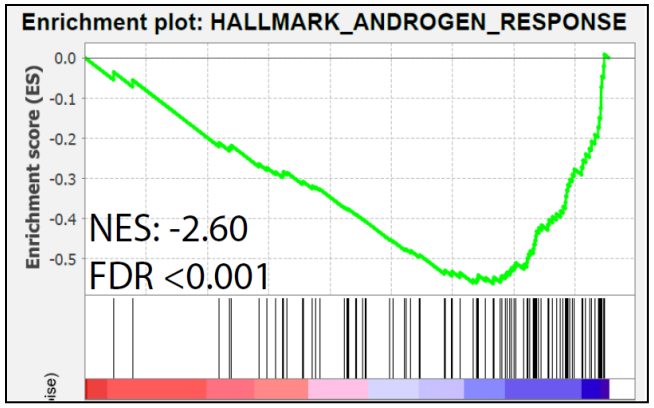
Aggarwal et al. CCR 2020, Aggarwal et al. AACR2019, Tsujikawa et al. AACR2017 + unpublished results

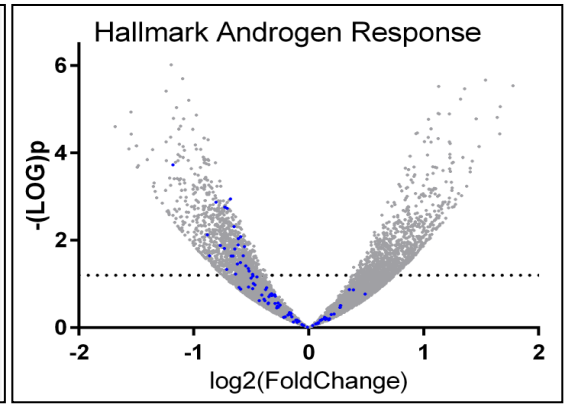
Detection of target engagement in 4 paired biopsies (Baseline, C3D1)

Inhibition of androgen and MYC signaling, modulation of BET-dependent genes

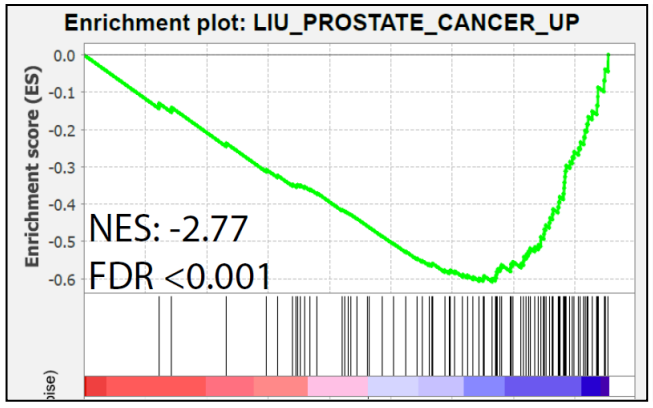
ZENITH EPIGENETICS

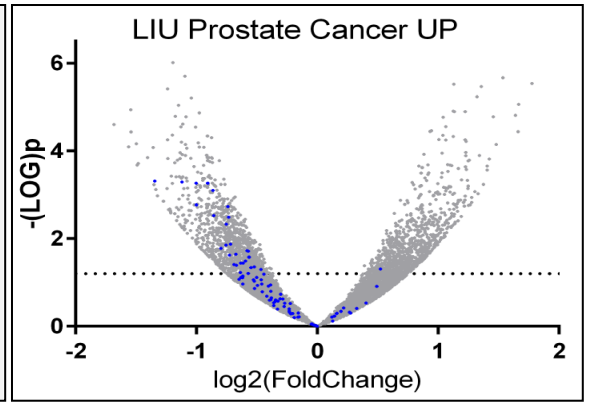
Inhibition of androgen signaling



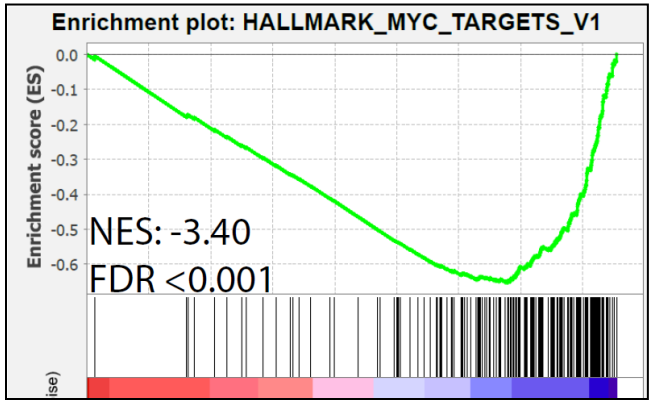


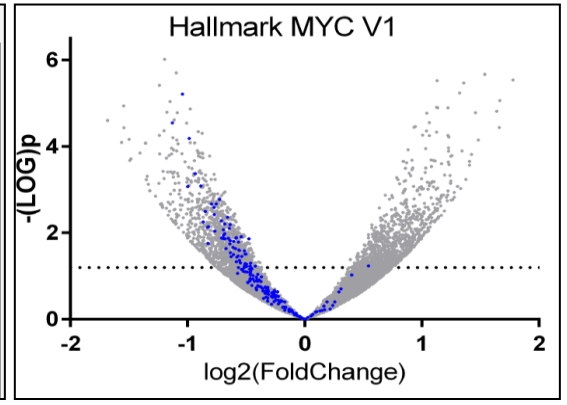
Inhibition of prostate cancer signature



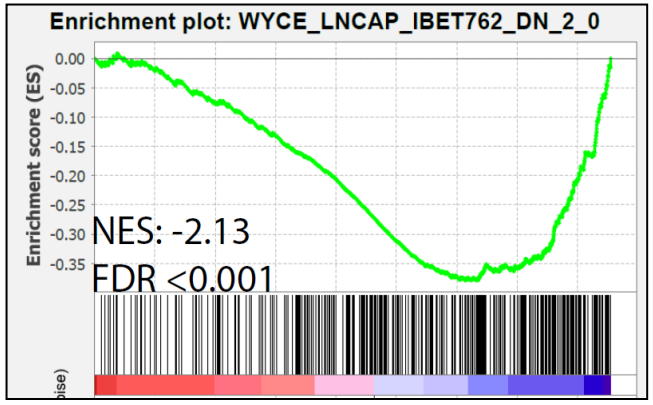


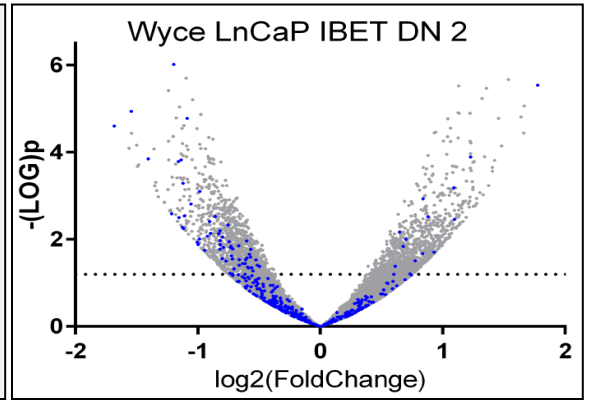
Inhibition of MYC signaling





Inhibition of BET-dependent genes





- **3/4 patients already receiving enzalutamide at time of Baseline biopsy**
- **Inhibition of several hallmarks of prostate cancer by ZEN-3694**

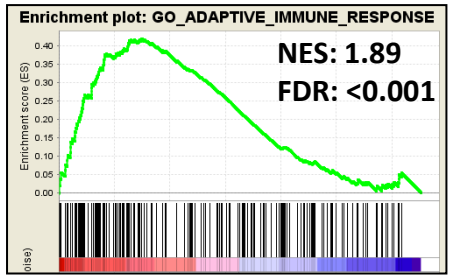
Aggarwal et al. CCR 2020

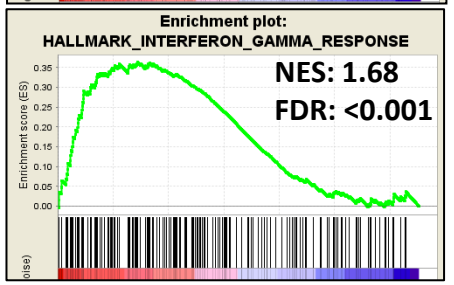
Evidence of an adaptive immune response On-Treatment in 2/4 paired biopsies

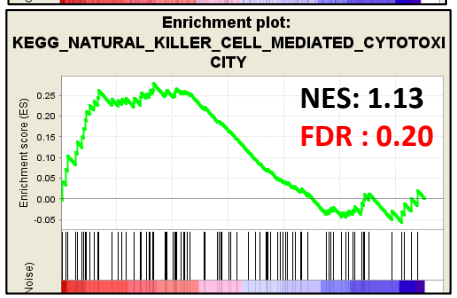
ZENITH EPIGENETICS

GSEA of paired biopsies

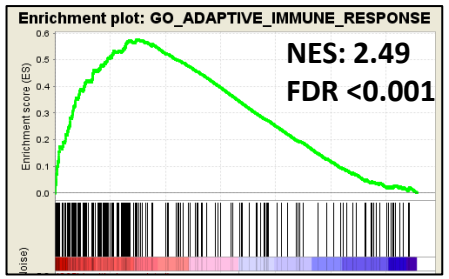
Patient A

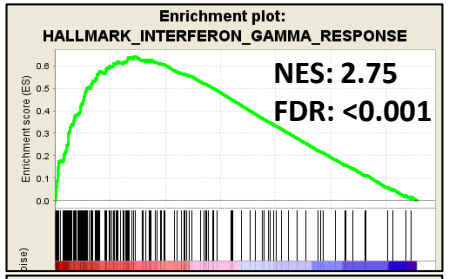


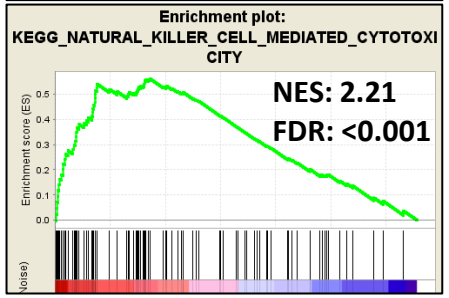


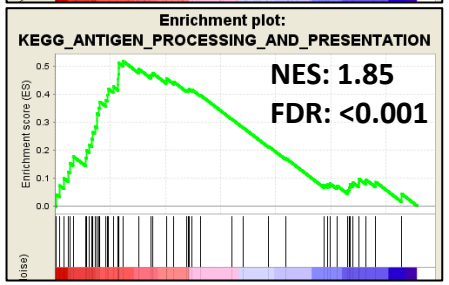


Patient B



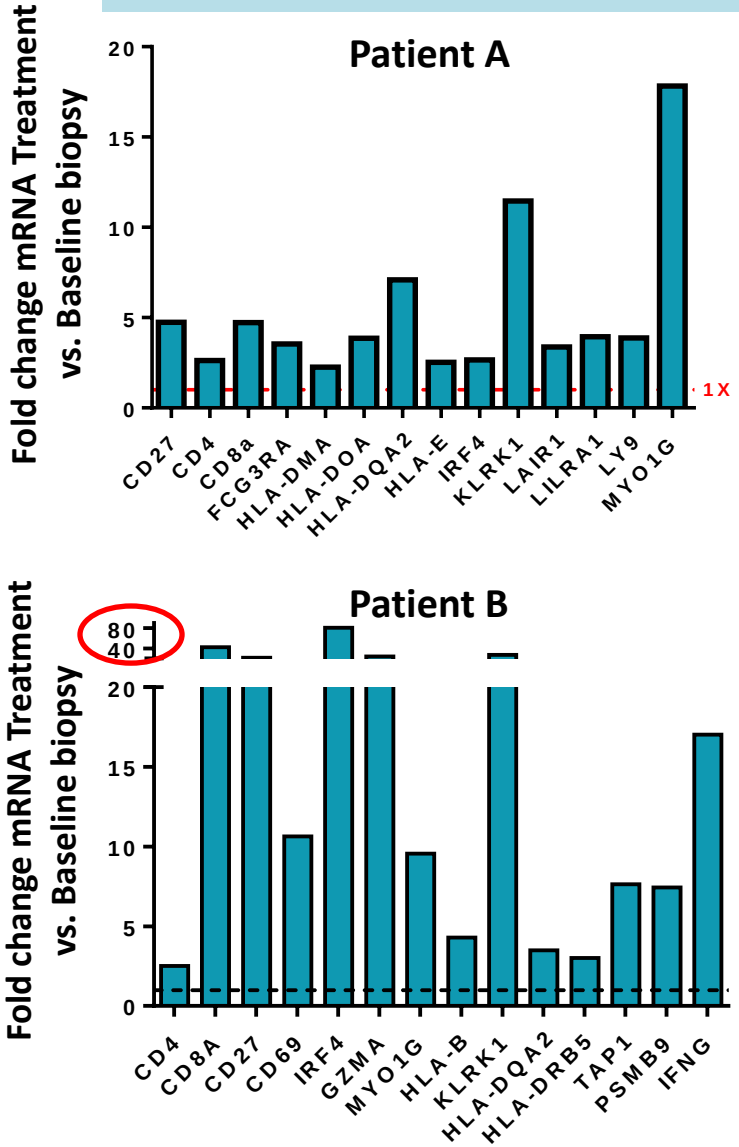






Unpublished results

Induction of genes involved in immune response On-Treatment



Overlap of induced genes between patients A and B

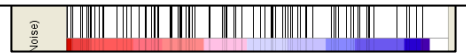
Immune Cell type	A	B
T and B lymphocytes (Antigen presentation/ T cell migration)	CD8a	
	CD4	
	CD27	
		LY9
	MYO1G	
	IRF4	
NK cells	KLRK1	
		FCGR3A
B cells		LILR1A
Leukocyte		LAIR1
Tumor NK receptor	HLA-E HLA-A	
Class II MHC	HLA-DRB5, HLA-DQA2, HLA-DOA, HLA-DOB, HLA-DMA	
Antigen processing presentation		TAP1, TAP2, PSMB8, PSBM9, IFNγ

Evidence of an adaptive immune response On-Treatment in 2/4 paired biopsies

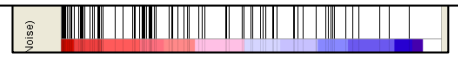
ZENITH EPIGENETICS

GSEA of paired biopsies

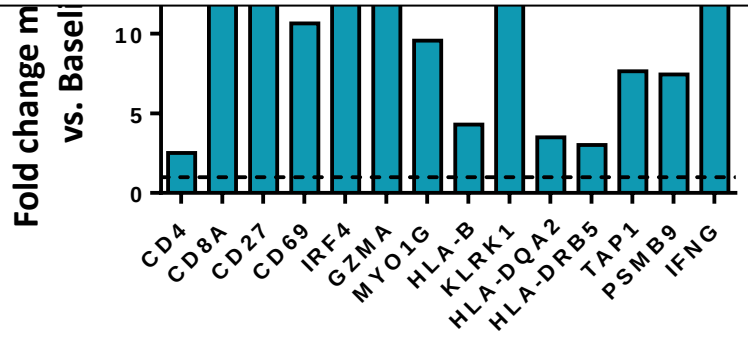
Patient A



Patient B



Induction of genes involved in immune response On-Treatment



Overlap of induced genes between patients A and B

Class II MHC	HLA-DRB5, HLA-DQA2, HLA-DOA, HLA-DOB, HLA-DMA	
Antigen processing presentation		TAP1, TAP2, PSMB8, PSBM9, IFNγ

ZEN-3694, Enzalutamide, and Pembrolizumab for the Treatment of Metastatic Castration-Resistant Prostate Cancer

ClinicalTrials.gov Identifier: NCT04471974

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Recruitment Status : Not yet recruiting
First Posted : July 15, 2020
Last Update Posted : July 15, 2020

See Contacts and Locations

Sponsor:
Rahul Aggarwal

Collaborators:
Zenith Epigenetics
Merck Sharp & Dohme Corp.
U.S. Army Medical Research and Development Command

Information provided by (Responsible Party):
Rahul Aggarwal, University of California, San Francisco

Unpublished results

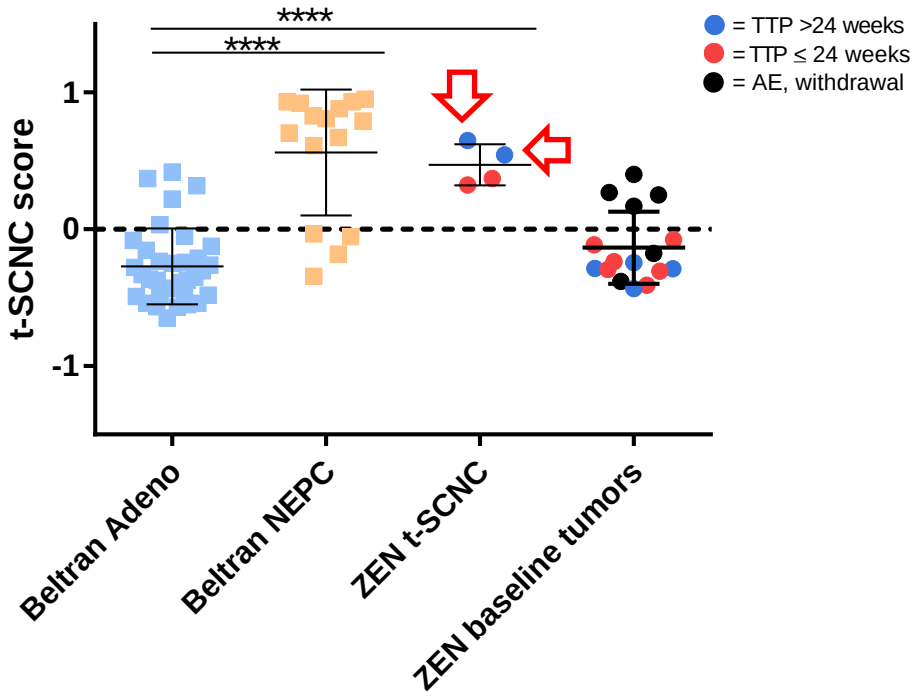
Detection of gene signatures of poor response to ARSI in patients with longer time on the trial

Aggarwal et al. PCF2019, CCR 2020 + unpublished results

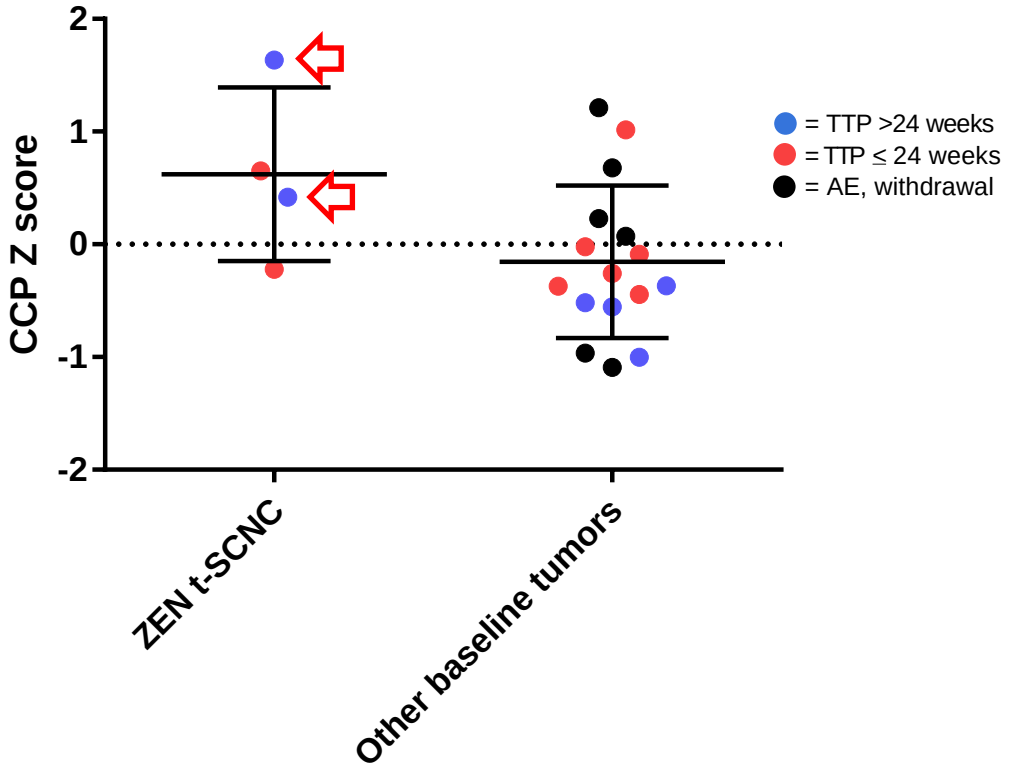
Signatures of enzalutamide resistance detected in two patients with longer time to progression (TTP > 24 weeks)

- **Treatment-induced small cell neuroendocrine prostate cancer (t-SCNC) is associated with poor prognosis on ARSI**
- **Cell cycle progression score (CCP) has been associated with poor responses to 1st line ARSI**

Tumor biopsies from 4 evaluable patients had t-SCNC signature



High CCP score associated with 2 t-SCNC tumors with long TTP



Two patients with long TTP had signatures of t-SCNC and high CCP associated with poor response to ARSI

ARSI = AR signaling inhibitor (enzalutamide, apalutamide, darolutamide, abiraterone)

Aggarwal et al. 2018, Abida et al. 2019, Aggarwal et al. PCF2019 + unpublished results

Analysis of CRPC patient biopsies shows loss of AR signaling and dependence associated with longer time to progression

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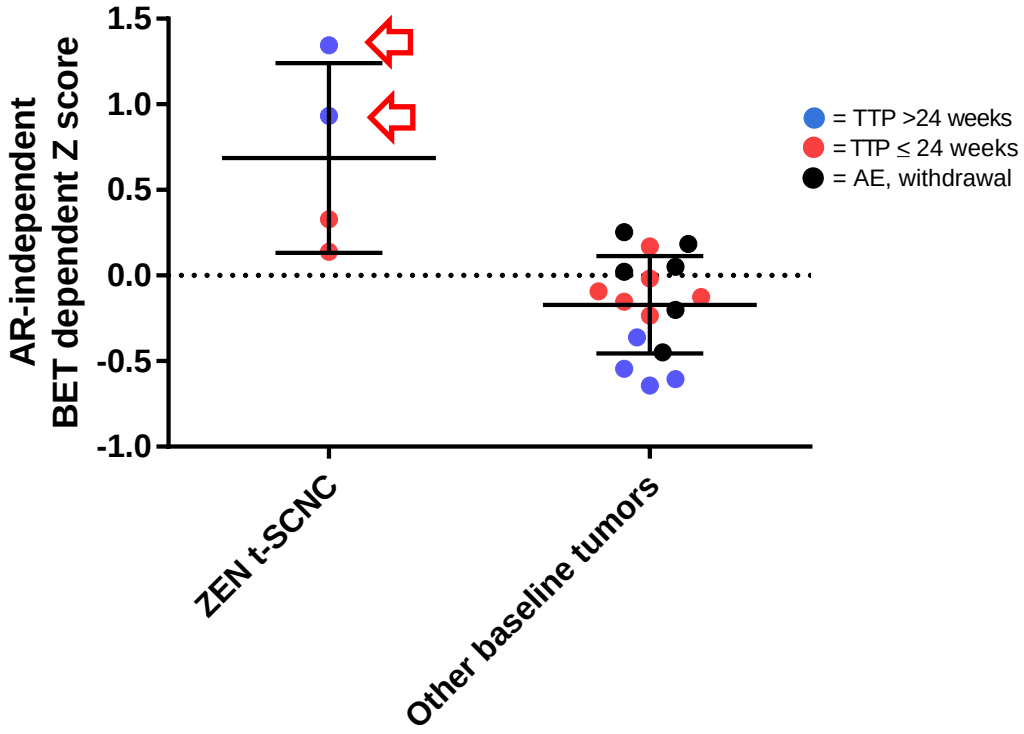
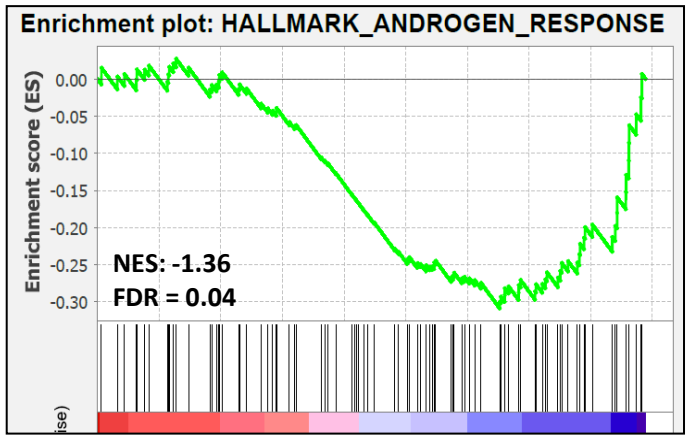
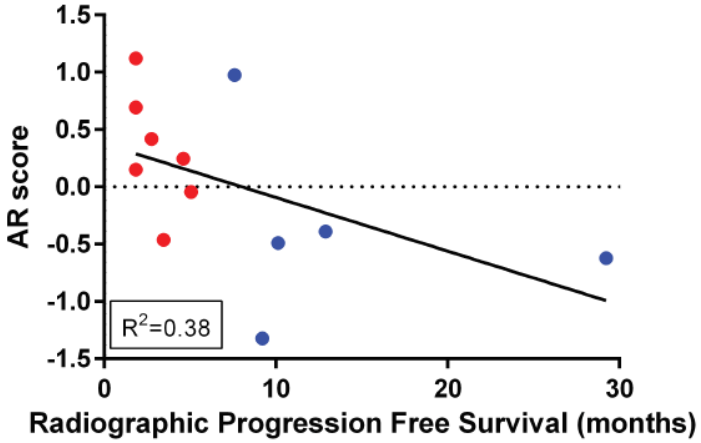
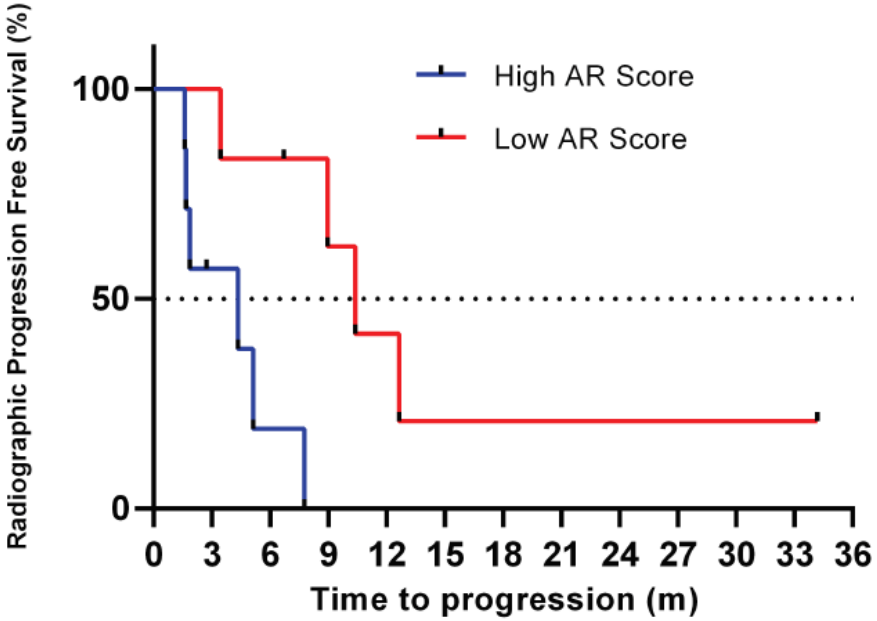
AR-independence/BET-dependence signature associated with t-SCNC tumors with long TTP



Association of lower AR signaling in baseline biopsies with longer rPFS





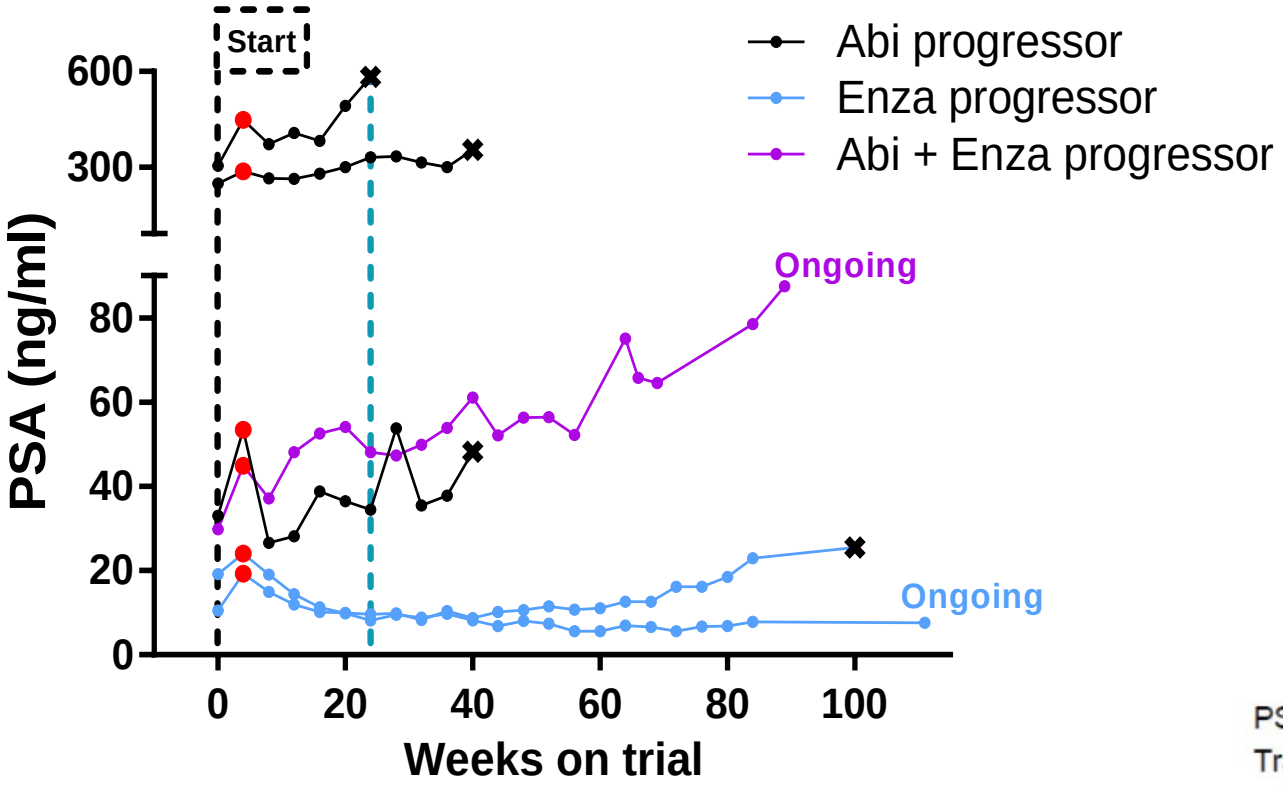


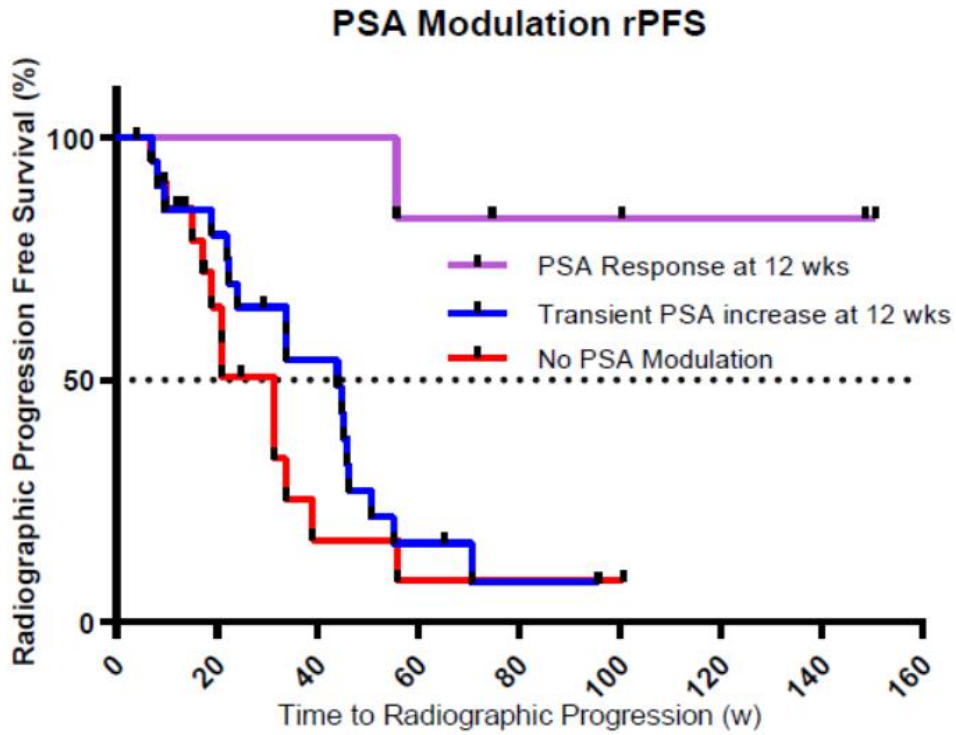
Aggarwal et al. PCF2019, CCR 2020, Coleman et al. 2019, unpublished results

Identification of PSA spikes as a candidate biomarker of response to ZEN-3694 + enzalutamide

Aggarwal et al. CCR 2020 + unpublished results

PSA spikes at either 4 or 8 weeks in several patients with longer TTP





PSA50 Response at 12wks	6	6	6	5	3	3	2	2	0
Transient PSA Inc at 12wks	21	16	10	3	1	0	0	0	0
No PSA Modulation	21	9	2	1	1	1	0	0	0

21/75 (28%) of patients with PSA spike

Median $rPFS_{PSA\ SPIKE}$ = 10.1 mo

Aggarwal et al. CCR 2020

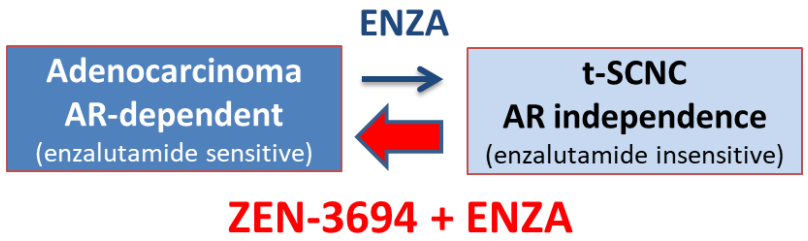
Conclusions

- **Combination of ZEN-3694 with ENZA was well tolerated with daily dosing**

⇒ Combination → right targeted agent
⇒ Patient population → chemo-naïve
⇒ BET inhibitor → moderate half-life

- **Evidence of clinical activity in AR-low and AR-independent patients with candidate predictive biomarkers**

⇒ PSA spikes at 4 or 8 weeks
⇒ t-SCNC, AR-independent/BET-dependent, CCP gene signatures



<u>Future clinical development of ZEN-3694:</u>

- **Phase 2 ZEN-3694 + enzalutamide + pembrolizumab in mCRPC patients** (initiation Q4 2020)

- **Phase 2 ZEN-3694 + PARPi talazoparib in TNBC patients <u>without</u> germline BRCA1/2 mutations (gBRCA1/2wt)**

⇒ Manageable combination, RP2D determined
⇒ Early results show promising activity (SABCS 2020)

- **Randomized study of ZEN-3694 + enzalutamide in prostate cancer patients** (early 2021)

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- **Patients and their family**

ZEN003694-002 Principal Investigators

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- Moon Chung (U. Washington)
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